REMARKS

Claims 22, 41, 62 and 64-68 are currently pending in the present application. Claims 41 and 68 have been amended herein. Support for the amendment of claim 41 may be found in the specification, at least, at page 3, second paragraph – page 4, line 4. Claim 68 was amended to correct an issue of improper antecedent basis and is fully supported by the prior claim set. No new matter has been added by way of the present claim amendments.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 68 stands rejected for lacking proper antecedent basis. In response to the outstanding claim rejection, Applicants have amended claim 68 to correct the antecedent basis of the basic medicine. Accordingly, Applicants respectfully request withdrawal of the outstanding rejection.

Rejection Under 35 U.S.C. § 102(b)

Claims 41 and 62 stand rejected under 35 U.S.C. § 102(b) as being anticipated by USP 5,013,557 to Tai (hereinafter "Tai").

Applicants have amended claim 41 by limiting the basic medicine to one that is not disclosed in Tai. Specifically, Applicants have amended claim 41 to recite that the basic medicine is donepezil hydrochloride. Thus, since Tai does not teach each and every element of the claimed invention, Tai cannot properly anticipate the presently claimed invention, within the meaning of 35 U.S.C. § 102(b). Withdrawal of the outstanding rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 22, 65 and 66 stand rejected as being rendered obvious by Tai in view of USP 5,464,612 to Matoba et al. (hereinafter "Matoba") and further in view of "The Rationale for E2020 as a potent acetylcholinesterase inhibitor" to Kawakami et al. (hereinafter "Kawakami").

Claims 64, 67 and 68 stand rejected as being rendered obvious by Tai in view of Matoba, and further in view of Kawakami, and further in view of JP 4-346937 to Morikazu et al. (hereinafter "JP '937").

Applicants respectfully traverse each of the outstanding rejections.

The Present Invention

The present invention is directed to an oral medicine preventing an unpleasant taste which comprises a mixture comprising a basic medicine (donepezil hydrochloride) having an unpleasant taste and an acidic polysaccharide, as recited in claim 22. In the present invention, the mixture is in a homogeneous blend and said basic medicine and acidic polysaccharide are in intimate contact in order to form an electric interaction and to prevent the basic medicine from dissolving in saliva. The present invention is also directed to a method of manufacturing as recited in pending claim 41.

Discussion of Cited Prior Art

In the outstanding Office Action, the Examiner has taken the position that the claimed invention (i.e., preventing an unpleasant taste by donepezil hydrochloride and carrageenan, etc.) is lacking inventiveness and is, therefore, easily within the skill in the art. Specifically, the Examiner states "The polymers soluble in the gastric fluids are polymers which bind to sucralfate

with taste masking properties and dissolve in gastric fluid." *See* Tai, col. 6, lines 26-55. Tai, at column 6, lines 36-44, discloses many compounds as useful in producing spray-dried microcapsules of sucralfate. However, there are no Examples using the referenced compounds. The compounds are proposed as being useful for producing spray-dried microcapsules of sucralfate, but are not disclosed as applicable to other medicaments.

Tai fails to show all of the requisite features of the instantly claimed invention, particularly the claimed electric interaction and homogeneous blend. This is due to a misunderstanding of the term "basic" medicine. The Examiner's reference in the Office Action to sucralfate as being a basic medicine is improper. Sucralfate is also generically known as "basic aluminum sucrose sulfate" and is an aluminum salt of an acidic medicine (sucrose sulfate).

Regarding Tai's disclosure of sucralfate, the effect of masking an unpleasant taste by adding donepezil hydrochloride and an acidic polysaccharide according to the claimed invention is due to the formation of an ionic complex by the positively-charged donepezil hydrochloride (a basic medicine) and the negatively-charged acidic polysaccharide. But in contrast to the present invention, and as described above, sucralfate is a basic aluminum sucrose sulfate having a negative charge, and therefore does not form a complex by an ionic interaction as is formed in the claimed invention. In fact, the mechanism for masking a bitter taste of sucralfate is different. The aluminum component (of a salt of sucralfate) and alginic acid are blended together, wherein moisture from water or from the oral cavity is taken in. The bitter substance (sucralfate) is present in the gel state, and the area of contact with the specific region of the tongue (which tastes the bitterness) is reduced. As a result, the bitterness can be prevented or reduced, but this

mechanism is completely different from the masking effects of the presently claimed invention. Since sucralfate is a negatively-charged compound, it never forms a complex by ionic interaction as is required by the claimed invention.

Accordingly, it is difficult to arrive at a composition preventing a bitter taste of the claimed invention from the Tai disclosure, in which donepezil hydrochloride (positively-charged) and carrageenan, etc., are homogeneously mixed. Moreover, neither Kawakami nor Matoba cure the deficiencies of Tai.

Kawakami gives no description of the unpleasant taste of E2020 to the patient and thus the Examiner is using Kawakami only for disclosing donepezil hydrochloride and is improperly combining Kawakami with the other references. The Examiner turns to Matoba to demonstrate that it was known in the art, at the time of the present invention, that basic drugs have a bitter taste and that the taste may be masked with a coating composition. However, the proposed combination of Tai, Kawakami and Matoba is based entirely on the Examiner's improper hindsight reasoning, as the present inventors were the first to discover the bitter taste of donepezil hydrochloride. Thus, those of ordinary skill at the time of the present invention would not have looked to Matoba, as presently suggested by the Examiner, because there was no recognition of the problem. The discovery of a problem is inventive even if once discovered, the solution is obvious. *In re Antonson*, 47 CCPA 740, 272 F.2d 948, 124 USPQ 132 (CCPA 1959).

Thus, for at least the reasons discussed above, the presently claimed invention is patentably distinct from the cited prior art references. Reconsideration and withdrawal thereof of each of the outstanding rejections are respectfully requested.

Response to Arguments

The Examiner has taken the position the evidence submitted in the Rule 132 Declaration filed on December 19, 2007 is not persuasive. The Examiner states in the Office Action at page 8, the second paragraph, that:

> "*[T]he test is not whether the specific bitterness of a drug was known at the time or not but whether . . . the invention* ***would have been obvious*** *to one of ordinary skill in the art at the time of the invention.*" (emphasis in original)

Applicants respectfully disagree with the Examiner's statement and respectfully direct the Examiner's attention to the M.P.E.P. §2141 which directly contrast the position taken by the Examiner. M.P.E.P. §2141 plainly states that:

> "In short, ***the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention***, and on what such a person would have reasonably expected to have been able to do in view of that knowledge." (emphasis added)

Thus, in view of the clear guidance of M.P.E.P. §2141, Applicants respectfully request that the Examiner reconsider the evidence submitted by Applicants in support of the patentability of the present invention. To facilitate the Examiner's consideration of the evidence, Applicants reiterate the explanation of the evidence herein.

<u>The Bitter Taste of Donepezil Hydrochloride</u>

Applicants have previously argued that the unpleasant, basic taste of donepezil hydrochloride was not known at the time the present application was filed, and that one of ordinary skill in the art was not aware of the bitter or unpleasant taste of donepezil hydrochloride before the priority dates of the present application. For instance, as previously explained, ARICEPT was in the form of a film tablet and thus it was not known that donepezil

hydrochloride itself had a bitter taste. Also, as further support of Applicants' position, Applicants previously submitted the following evidence:

- **Evidence A**: excerpt from the *Instruction Manual for Japanese Pharamcopeia* (13th Ed. 1996), together with an English language translation thereof (3 pages total);
- **Evidence B**: excerpt from *Modern Pharmaceutics* (Third Ed. 1996);
- **Evidence C:** excerpt from the *Technical Report of IEICE OME 2000-80*, titled "Quantification of Taste of Medicines with a Taste Sensor" (pages 125-130, include English language Abstract on page 125); and
- **Evidence D:** excerpt from *Pharm. Tech. Japan*, Vol. 17(9), pp. 31-33 (2001).

As previously stated, Evidence A shows a coated tablet as including a film-coated tablet and a sugar-coated tablet, wherein the coating serves multiple purposes. Evidence B shows that a "coated tablet" means coating of tablets, including film-coating, that is carried out for the purpose of masking an unpleasant taste, masking an unsightly appearance of uncoated tablets, increasing patient acceptability, and preventing degradation caused by moisture, air or light. Evidence C shows that the bitter taste of donepezil hydrochloride was first revealed by Eisai Co., Ltd. And Evidence D shows the first public exposure to the name of donepezil hydrochloride, wherein, e.g., Figure 5 reveals that donepezil hydrochloride has a very unpleasant taste.

Thus, Applicants previously provided Evidence labeled as A-D showing that one of ordinary skill in the art was not aware of the bitter or unpleasant taste of donepezil hydrochloride before the priority dates of the present application (March 28, 1997, which is the priority date of one of the corresponding Japanese applications, and March 26, 1998, which is the filing date of

the PCT application). Applicants previously provided the following additional explanation regarding Evidence A-D.

Evidence A and the English Language Translation of Evidence C

The evaluation of the taste of donepezil hydrochloride was for the first time presented at the conference in August 2000. This revelation regarding the bitter taste was disclosed by Applicants as shown in Evidence A (edited by the institute in August 2000). However, the name of donepezil hydrochloride was not specified at that point in time as can be seen in Evidence C.

In the abstract of the first page of Evidence A, the method of quantification of taste of a medicine is disclosed. The name of donepezil hydrochloride is not specified even in this literature. In Evidence C, the description "Model drug substance: MDHC1 (basic hydrochloride)" shown in Table 2 (at page 3 of the English version) as a medicament used in the described experiment is donepezil hydrochloride. Also, as is shown in Figs. 2, 3, 4, 7 and in Table 4 of Evidence C, donepezil hydrochloride is described as having an extremely bitter taste.

English Language Translation of Evidence D

It was for the first time disclosed by Applicants, as shown in Evidence D (which is edited in September 2001), that donepezil hydrochloride has an unpleasant taste, wherein the name "donepezil hydrochloride" is first revealed. Also, Applicants note that "donepezil" is described in Figures 4 and 5 (see pages 34 and 35, respectively, of the Japanese text). It also is shown in these figures that donepezil hydrochloride has an extremely bitter taste (see also section 2.2.2 at pages 16-17 of the English language version). Finally, Applicants describe in their own specification that donepezil hydrochloride has an extremely bitter taste, wherein such a description is relying on the experimental results of Evidence D.

Discovery of a Problem Can Be Basis for Patentability

Applicants respectfully submit that the discovery of the problem itself can be a basis for patentability. Specifically, the Federal Circuit has held that the invention as a whole is not restricted to the specific subject matter claimed, but also embraces its properties and the problem(s) it solves. [T]he invention as a whole is not restricted to the specific subject matter claimed, but also embraces its properties and the problem(s) it solves. *In re Wright*, 6 USPQ2d 1959, 1962 (Fed. Cir. 1988) ("The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered"); *In re Sponnoble*, 160 USPQ 237 (CCPA 1969). In other words, discovery of a problem is inventive even if once discovered, the solution is obvious. Moreover, "[i]t should not be necessary for this court to point out that a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. 103." *In re Antonson*, 47 CCPA 740, 272 F.2d 948, 124 USPQ 132 (CCPA 1959).

Here, Applicants were first to discover the problem of the bitter taste of donepezil hydrochloride. Thus, the proposed combination of prior art references (i.e., Tai in view of Matoba and further in view of Kawakami) is improper, because a person of ordinary skill in the art at the time of the present invention would not have known of the problem of the bitter taste of donepezil hydrochloride and thus would not have sought to treat the unknown problem. That skilled artisan would not refer to, e.g., Tai if that person is not aware of the problem.

Since objective evidence can rebut the Examiner's allegation of obviousness, Applicants respectfully request reconsideration of the evidence presented in support of the patentability of the present invention.

Obviousness-Type Double Patenting

Claims 22, 41, 62 and 64-68 stand rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6 and 12 of USP 6,576,677 to Ukai et al. (hereinafter "Ukai") in view of Tai.

Applicants respectfully traverse. Applicants respectfully submit that the presently claimed invention is patentably distinct from the Ukai in view of Tai because the mechanism by which the present invention prevents the bitter taste of donepezil hydrochloride is different than that of Ukai in view of Tai.

The mechanism of preventing a bitter taste of donepezil hydrochloride in the claimed invention is as follows:

Due to the ionic interaction between donepezil hydrochloride (positively-charged) and the specified acidic polysaccharide, such as carrageenan (negatively-charged), a water-insoluble ionic complex is formed and thereby a strong masking advantage of preventing a bitter taste is obtained. This result is due to the inhibition of elution of donepezil hydrochloride being a basic medicament into water or saliva. Thus, the contact of the basic medicament with the specific region of the tongue which senses bitter taste is almost lost and thereby the bitter taste is prevented.

Ukai discloses a mixture of donepezil hydrochloride (positively-charged) and polyvinyl pyrrolidone to form a water-soluble chelate by the following mechanisms to prevent bitter taste:

Polyvinyl pyrrolidone forms a water-soluble chelate (not insoluble) and the molecular weight thereof is increased. The effect of preventing bitter taste is due to inhibition of tongue cells in the oral cavity that sense bitter taste by the increased molecular weight of the formed chelate. The pyrrolidone group of polyvinyl pyrrolidone has "–O–" which traps donepezil hydrochloride (positively-charged) being a basic medicament as a chelate like pyrrolidone–O–donepezil hydrochloride–O–pyrrolidone.

Thus, it is apparent from the above descriptions that the presently claimed invention is patentably distinct from the cited combination of references. Accordingly, reconsideration and withdrawal are respectfully requested.

CONCLUSION

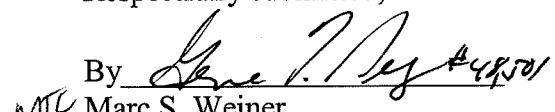
In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

Dated: September 16, 2008

Respectfully submitted,

By 
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